Drug Resistant Tuberculosis

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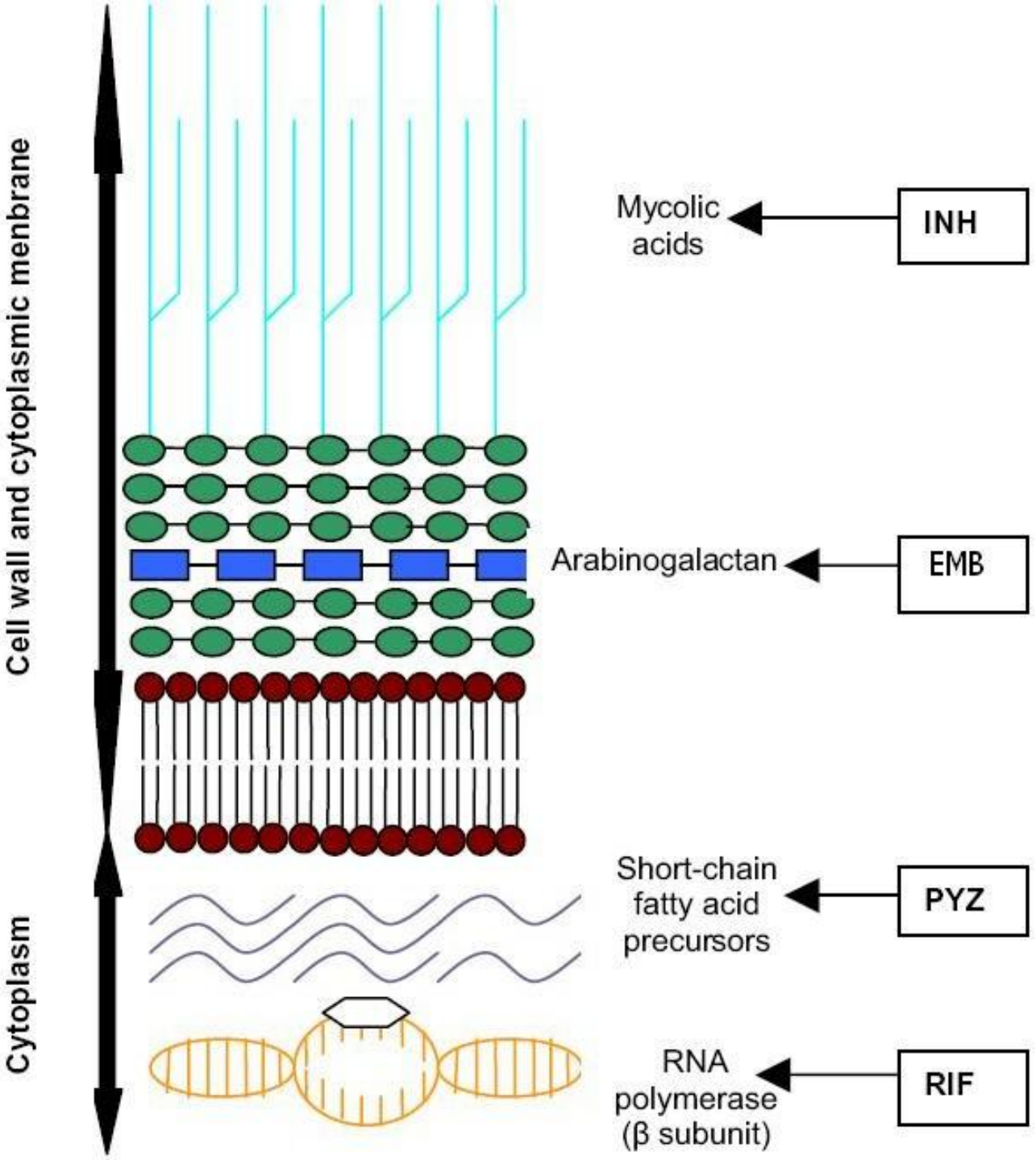
Goals for Today

- What is Drug Resistant TB?
- Where did DR TB come from?
- How do you prevent it?

TB Medications

- 1944 Streptomycin
- 1946 para-aminosalicylic acid
- 1952 Isoniazid
- 1954 Pyrazinamide
- 1955 Cycloserine
- 1962 Ethambutol
- 1963 Rifampin


Cell wall and cytoplasmic membrane
Cytoplasm
Mycolic acids
INH
Arabinogalactan
EMB
Short-chain fatty acid precursors
PYZ
RNA polymerase (β subunit)
RIF

Definition of Drug Resistance

- If more than 1% of the population grows at a critical concentration of a drug
- Critical Concentration of a drug
  - The level of a drug that inhibits a wild-type M. tb strain, but does not appreciably suppress the growth of a resistant strain

Critical Concentration

The lowest concentration of a drug that

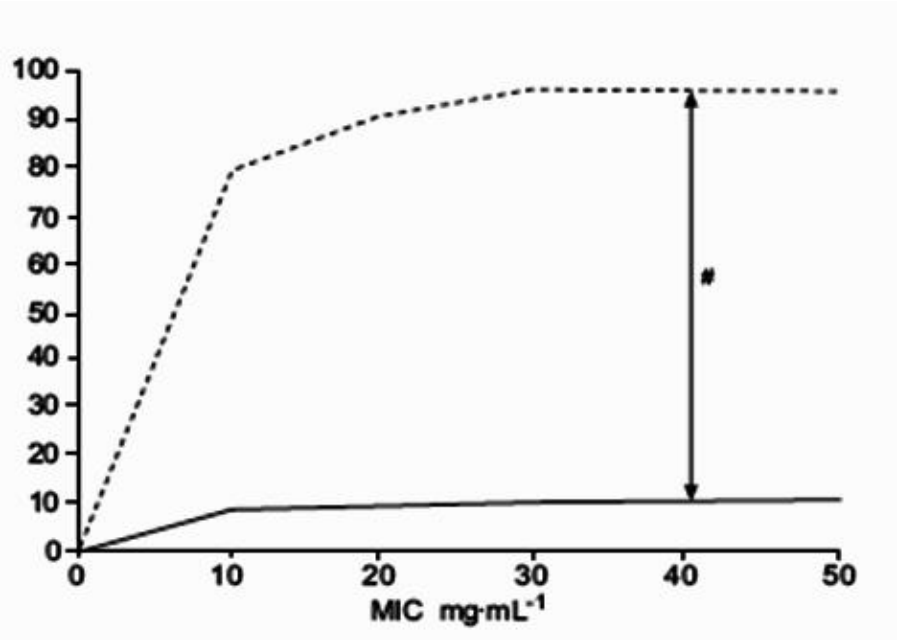
- **Inhibits growth of all susceptible strains**

AND

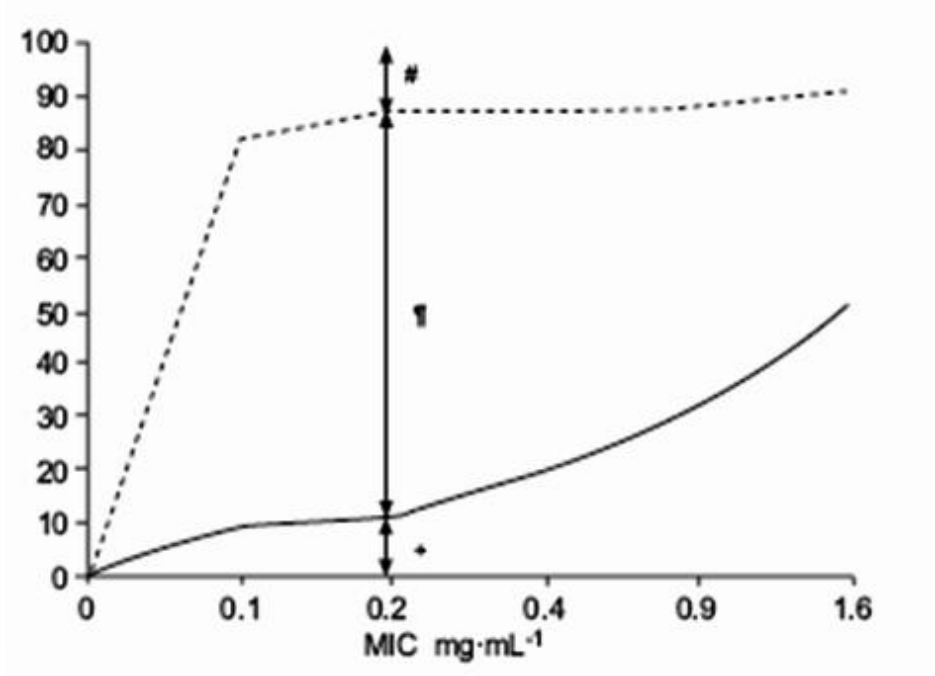
- **Allows growth of all resistant strains**

Critical Concentrations

Rifampin



Isoniazid



S.J. Kim. 2005. Eur Respir J 25:564.

Drug Resistant TB

- Monoresistant
- Multidrug Resistant (MDR)
- Polydrug Resistant
- Extensively Drug Resistant (XDR)
- Totally Drug Resistant (TDR)

Drug Resistance

- Monodrug Resistance
  - Resistance to only one drug
  - If organism is resistant to PZA, think M. bovis
- Multidrug Resistance
  - Resistant to both Isoniazid and Rifampin
- Polydrug Resistance
  - Resistant to more than one drug, but not both INH and Rifampin
  - INH and EMB, Rifampin and EMB, INH and SM

Extensively Drug Resistant TB
XDR

1) Resistant to INH and Rifampin
2) Resistant to any one of the Fluoroquinolones
3) Resistant to any one of the injectables
   – Amikacin, Kanamycin, Capreomycin

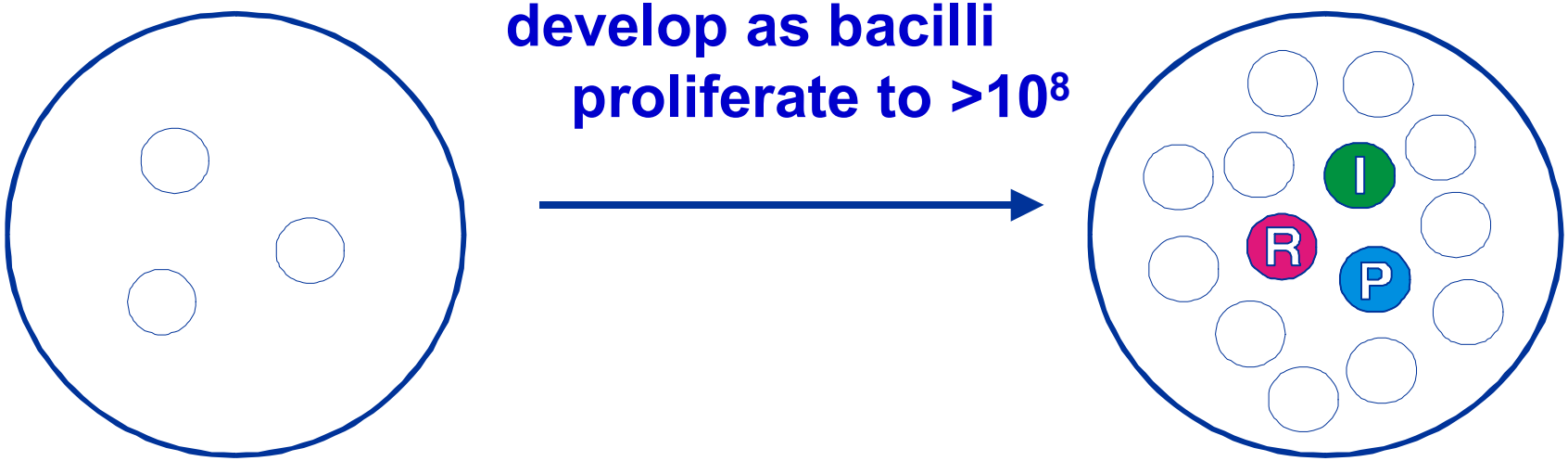
Totally Drug Resistant TB
TDR

- Resistant to all of the first and second line anti-Tuberculosis drugs
- Found in Italy and S. Africa already!

Drug Resistance

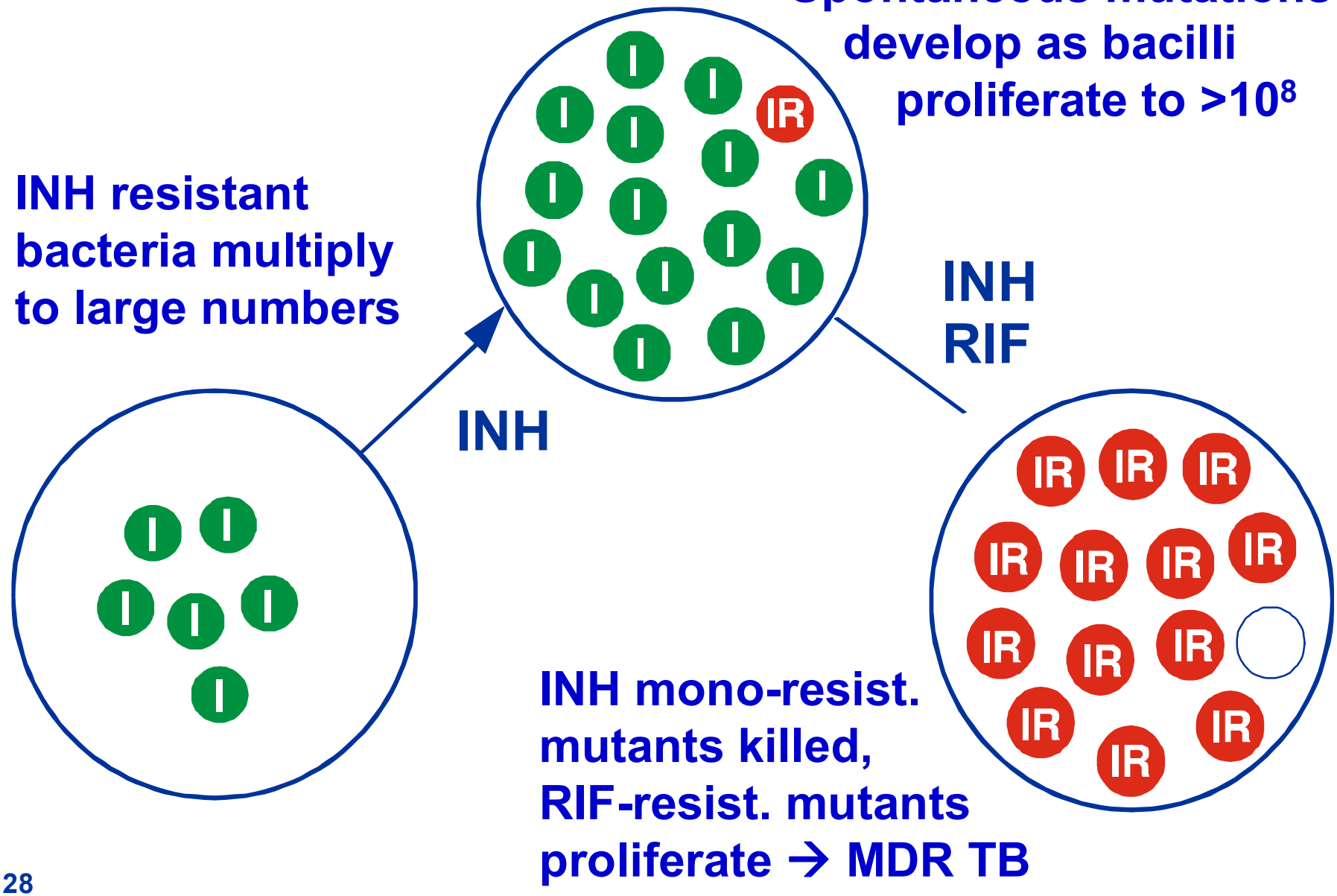
- Primary Drug Resistance
  - Resistant TB found in a person who has never been treated with anti-TB medications
  - Individual inhaled a resistant organism
- Secondary or Acquired Drug Resistance
  - Resistant TB found in a person who has been treated with anti-TB medications before for at least one month
  - The organism was made resistant by poor medical management of the patient

Spontaneous mutations develop as bacilli proliferate to >10^8

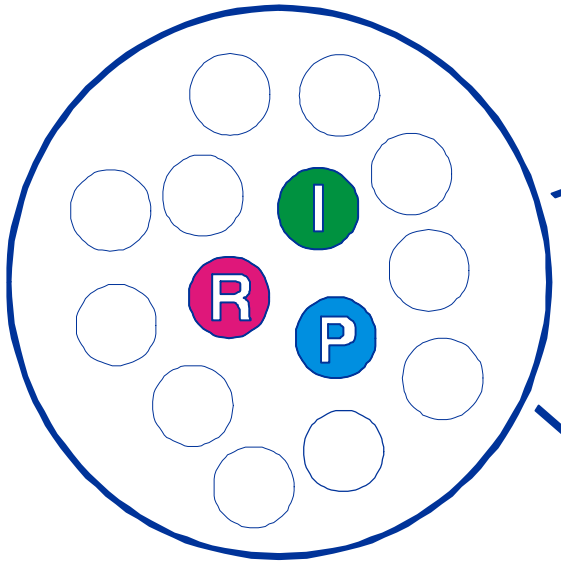


Drug	Mutation Rate
Rifampin	10^{-8}
Isoniazid	10^{-6}
Pyrazinamide	10^{-6}

108=100,000,000= one hundred million

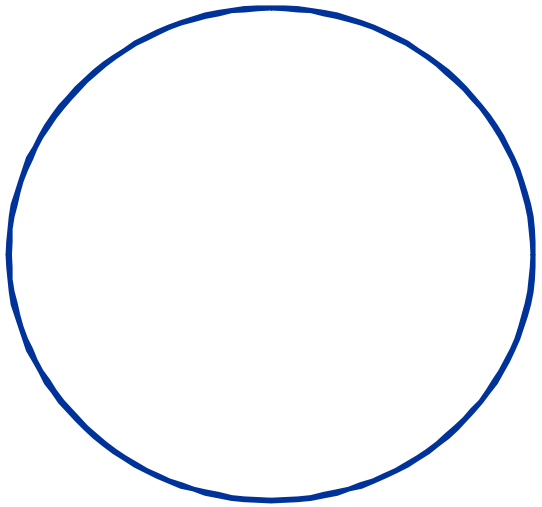

Spontaneous mutations develop as bacilli proliferate to >10^8
INH resistant bacteria multiply to large numbers
INH
INH
RIF
INH mono-resist. mutants killed, RIF-resist. mutants proliferate → MDR TB
IR

Drug-resistant mutants in large bacterial population



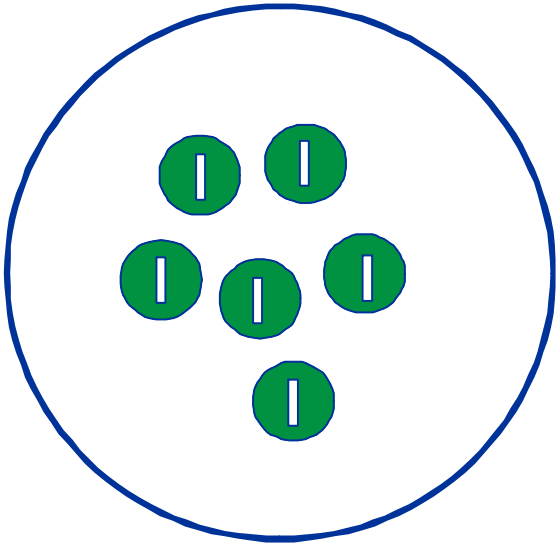
INH
RIF
PZA

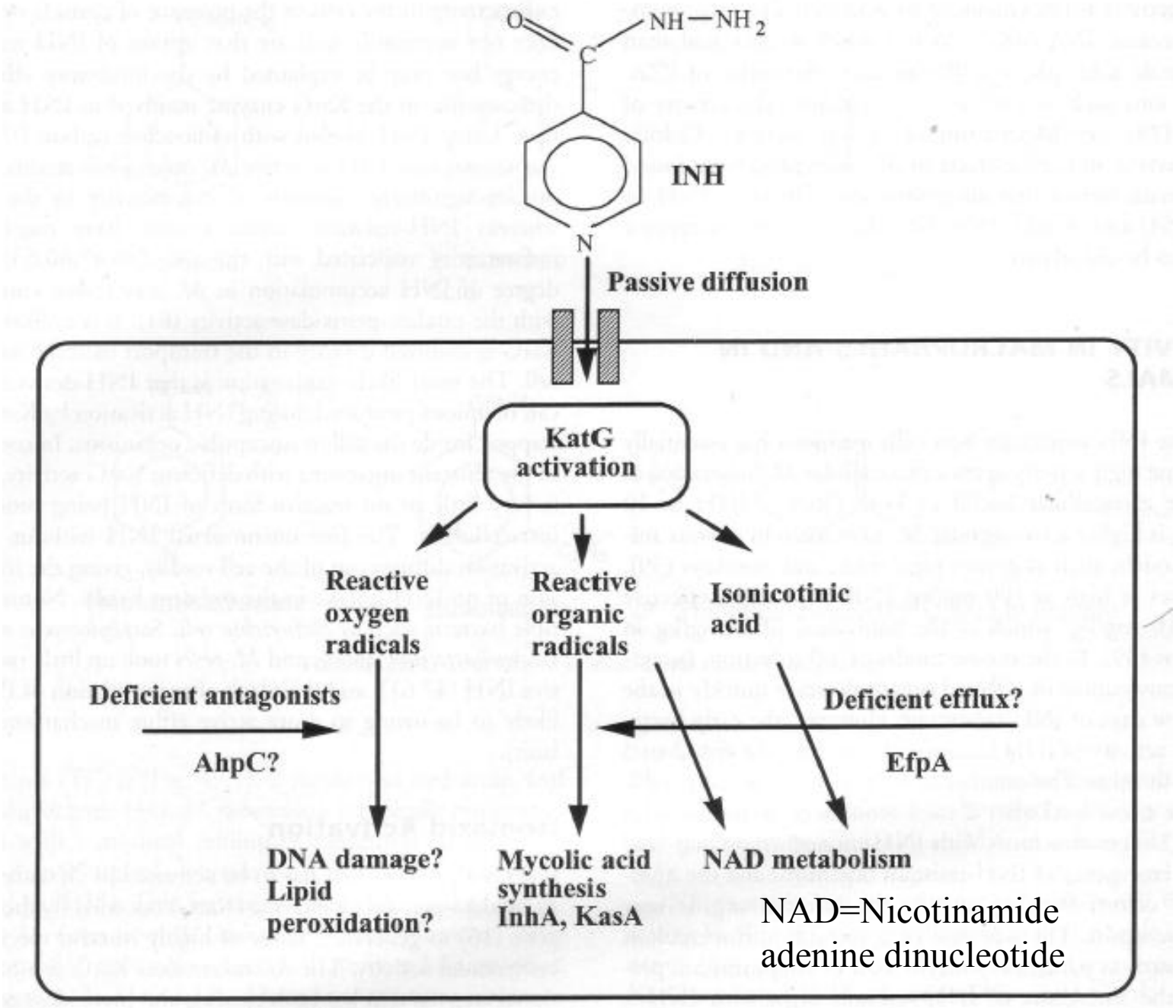
Multidrug therapy:
No bacteria resistant to all 3 drugs



INH

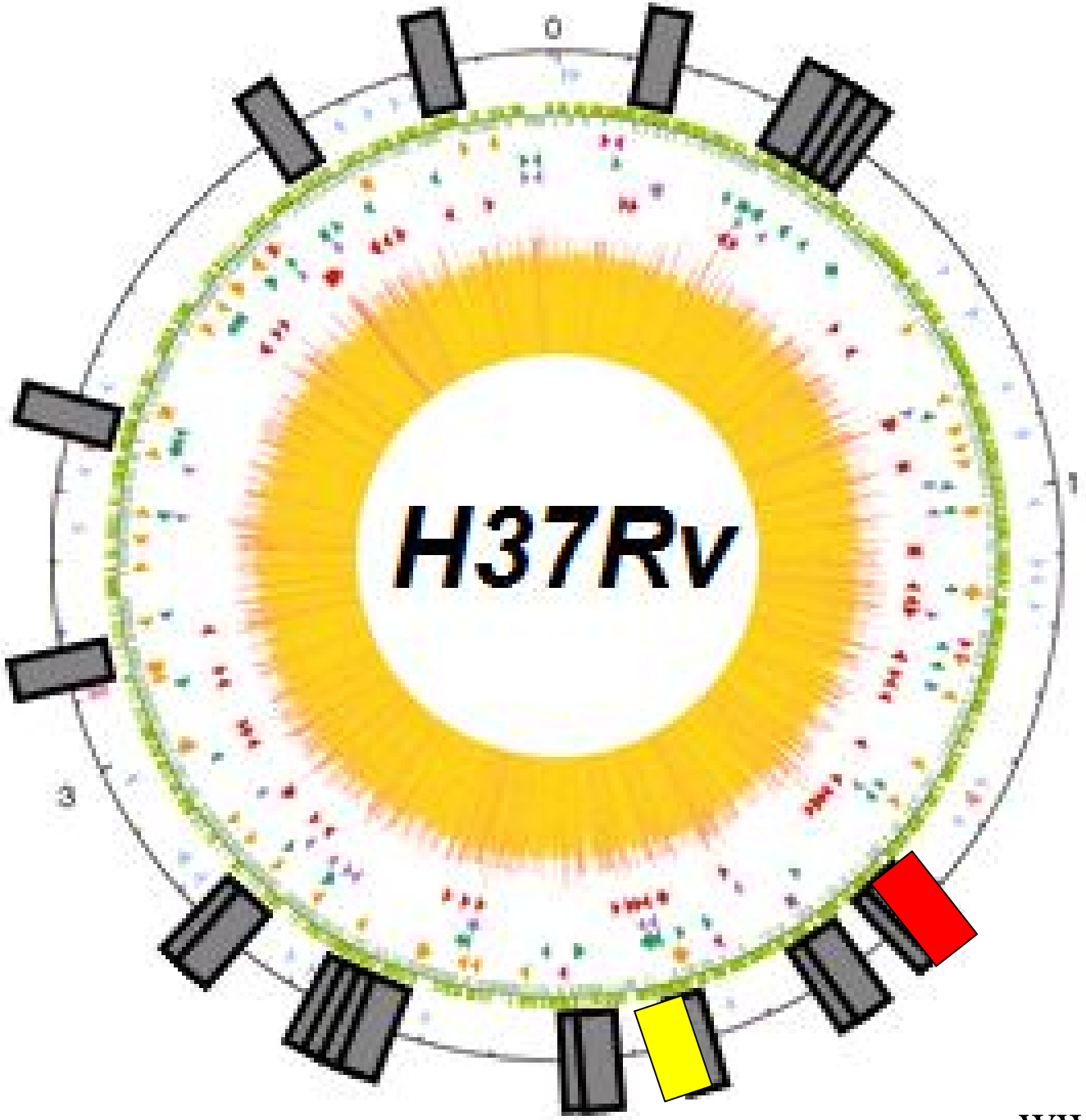
Monotherapy: INH-resistant bacteria proliferate





NAD=Nicotinamide adenine dinucleotide

Rom & Garay, 2nd Ed. Pg. 742



Isoniazid-

inhA *KatG*

and many others

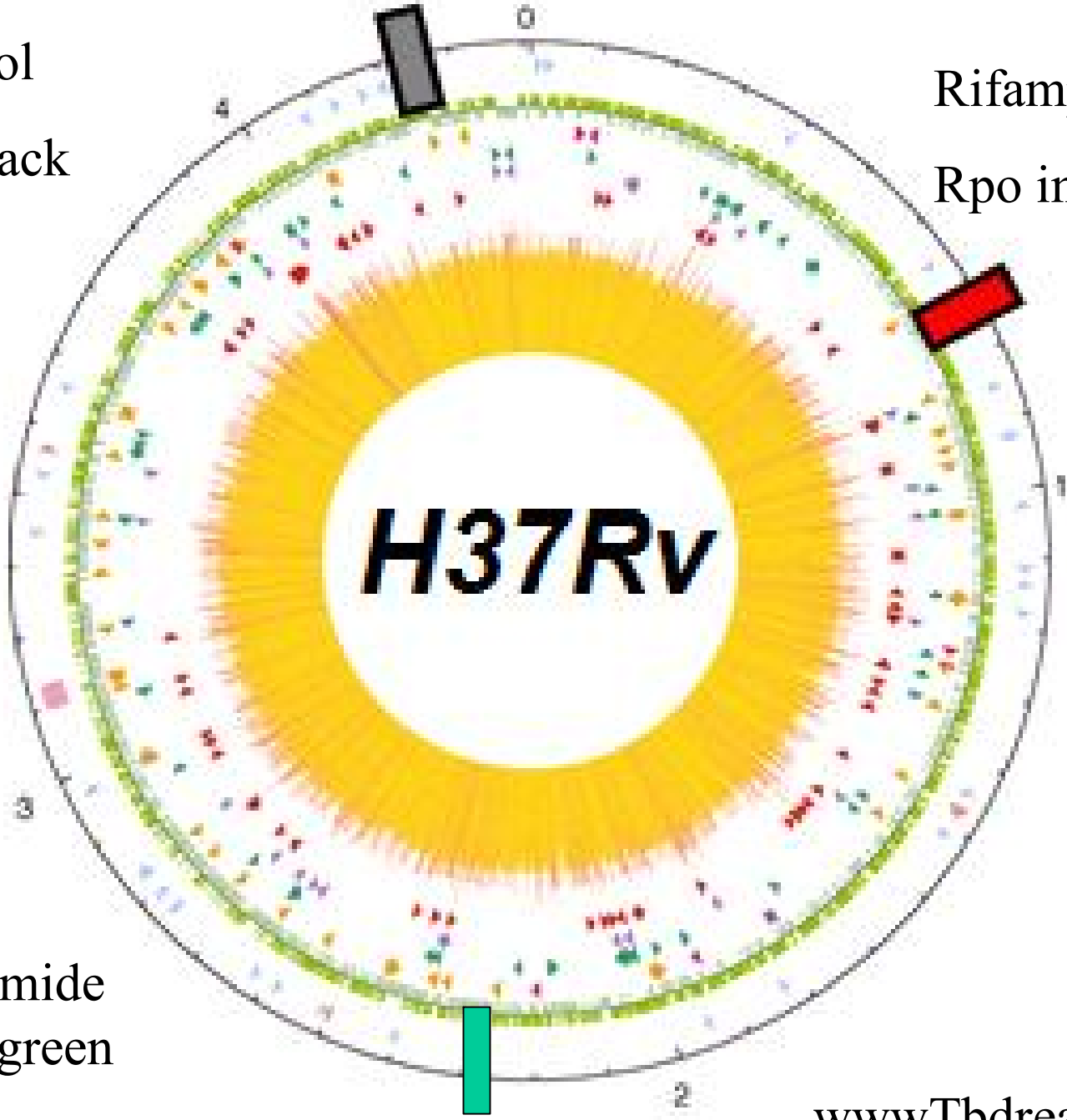
www.Tbdreamdb.com

Ethambutol

Emb in black

Rifampin-

Rpo in red

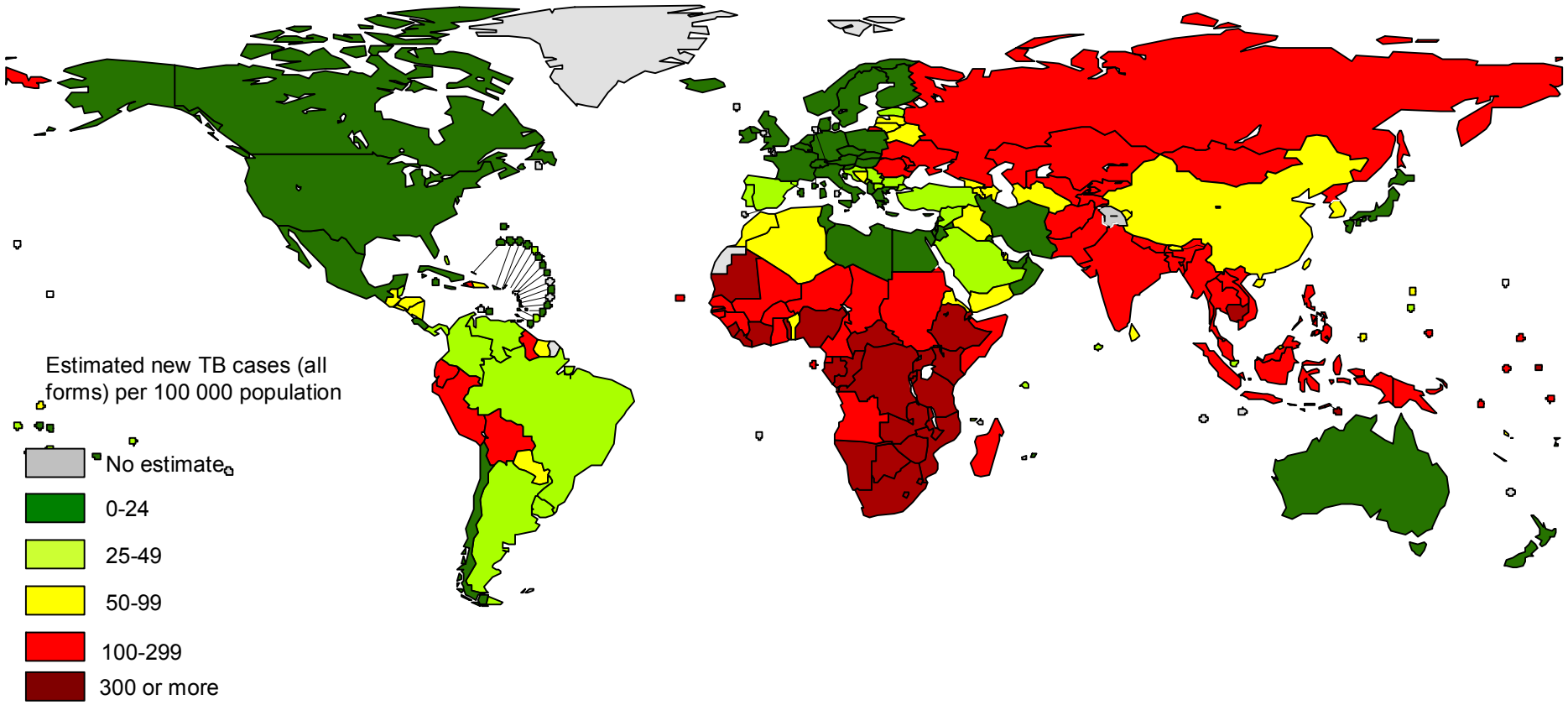


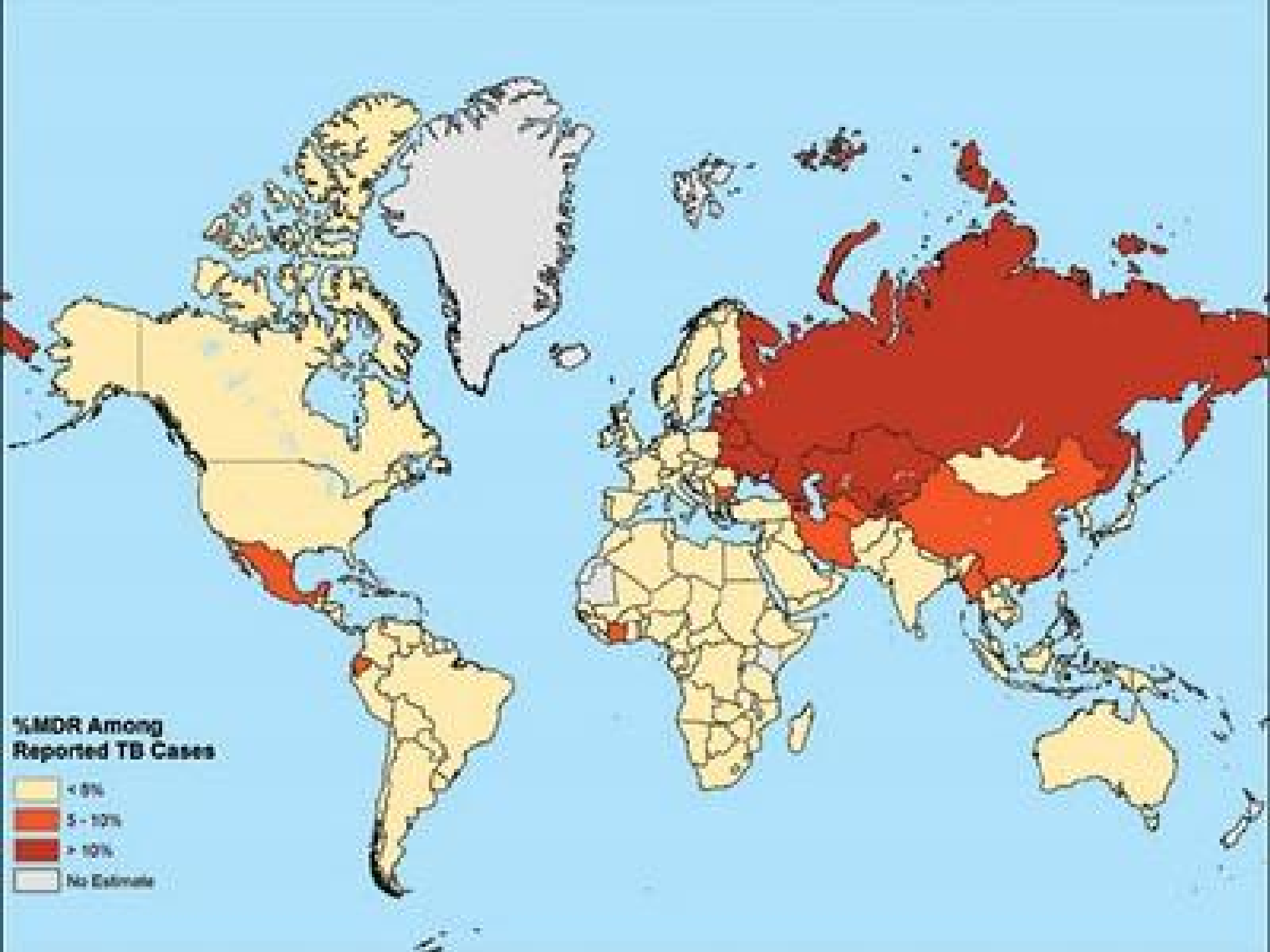
Pyrazinamide
pncA in green

wwwTbdreamdb.com

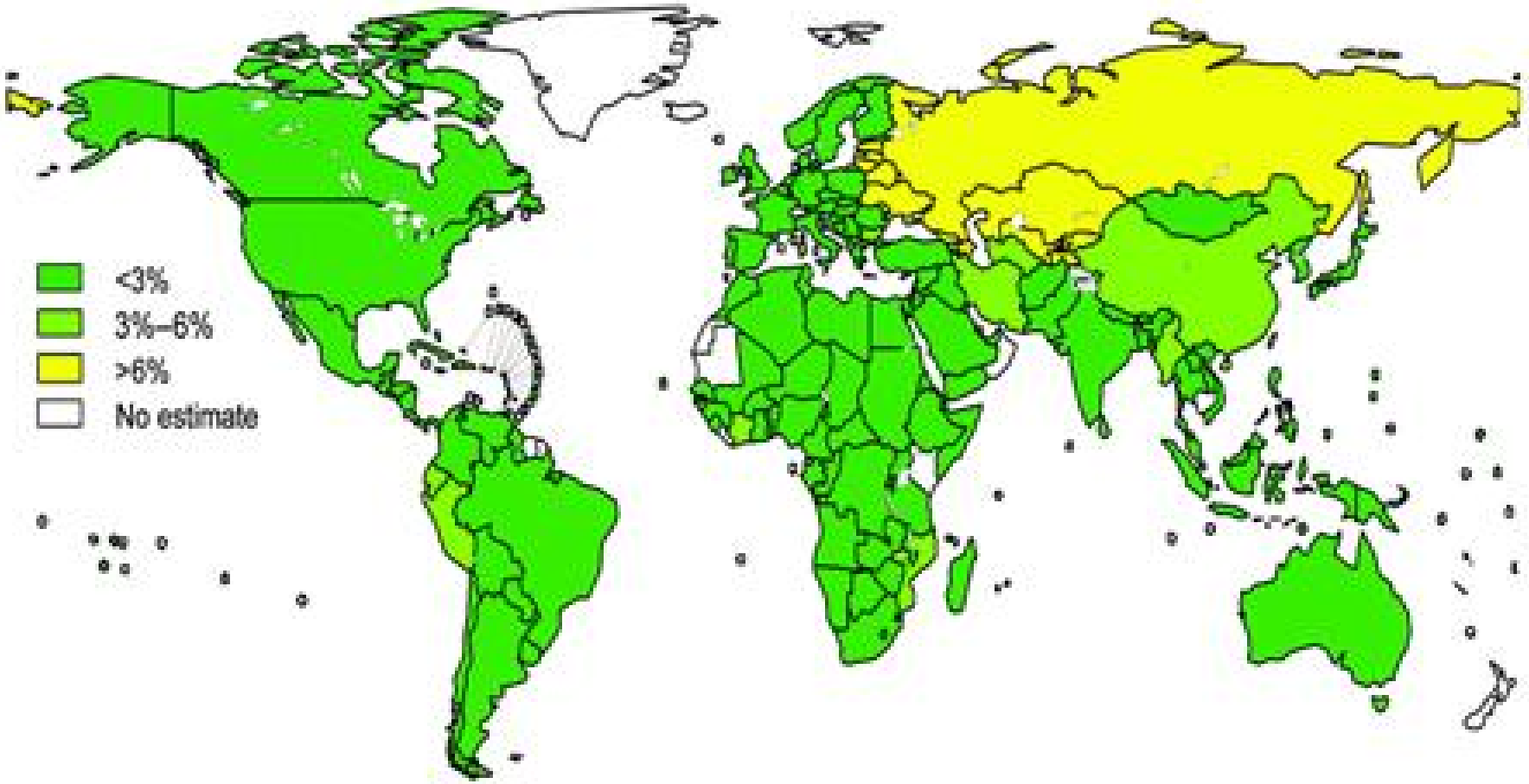
USAID
FROM THE AMERICAN PEOPLE

Highest TB rates per capita: Africa



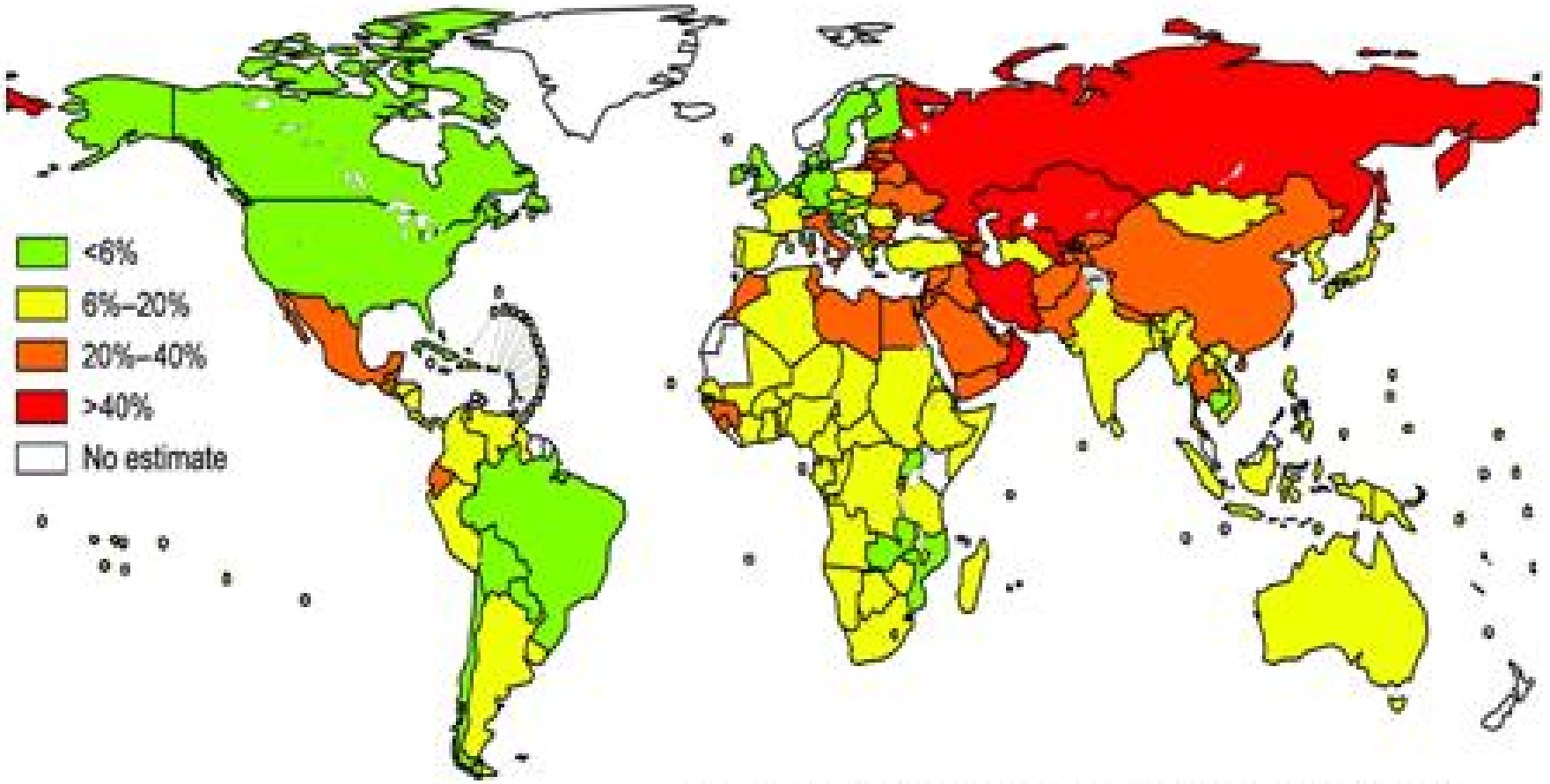

%MDR Among
Reported TB Cases
< 5%
5 - 10%
> 10%
No Estimate

Distribution of MDR-TB Rates Among New Cases



Source: Zignol M, et al. JID 2006:194:479

Distribution of MDR-TB Rates Among Previously Treated Cases



Source: Zignol M, et al. JID 2006:194:479

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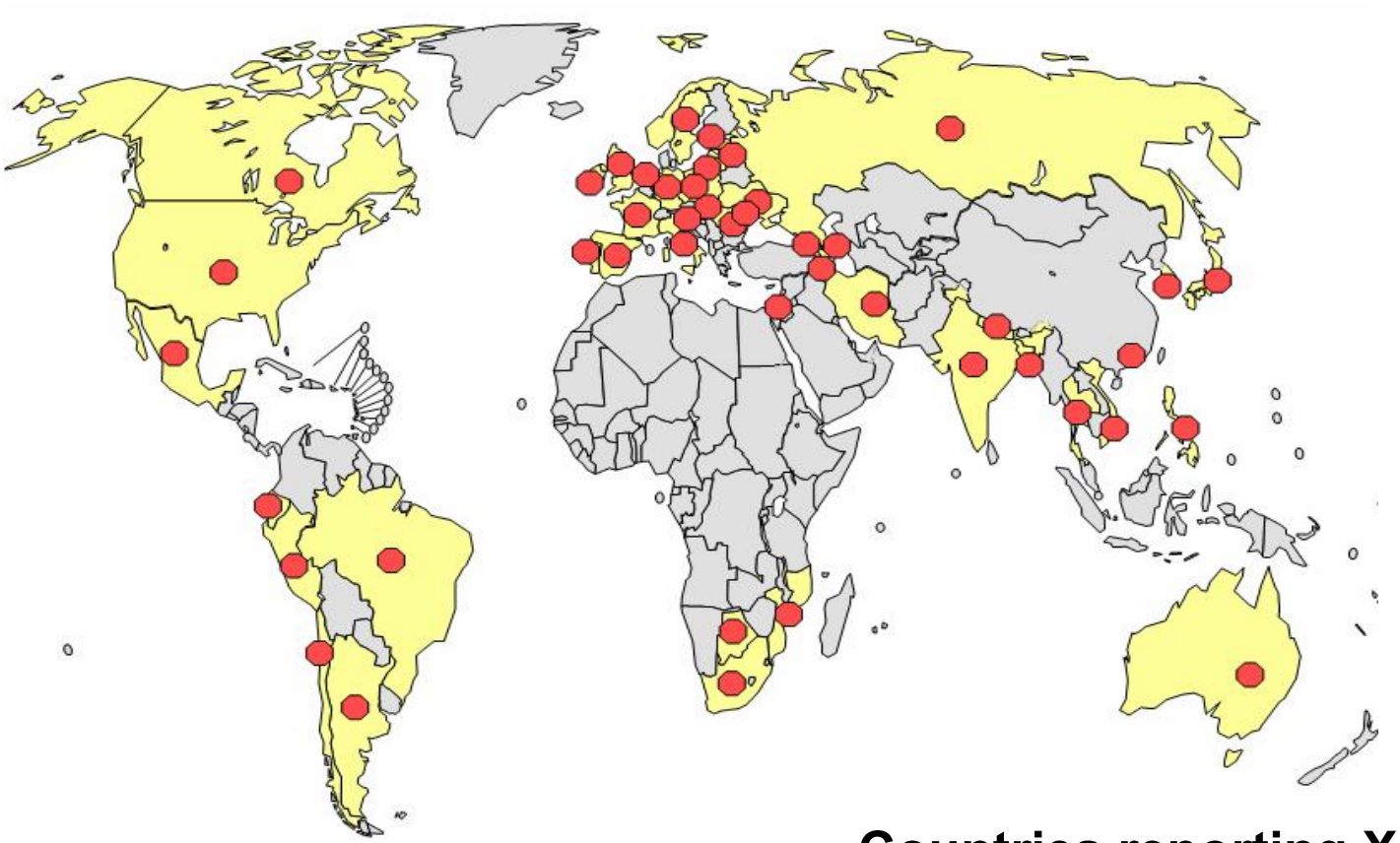
XDR TB Confirmed in 45 Countries



Source: WHO Anti-TB Drug Resistance in the World Report 4, 2008

Countries reporting XDR TB as of Feb 2008

XDR-TB Cases in the United States (Initial DST), 1993–2007*

*Reported incident cases as of 7/18/07

Causes of Drug Resistance by TB-Healthcare Providers

- Poorly organized or funded TB Control Programs
- Inappropriate, poor or no guidelines
- Non compliance with guidelines
- Poor training
- No monitoring of treatment
- Errors in prescribing; wrong dose, wrong frequency, not enough different medications

WHO 2008

Causes of Drug Resistance Laboratories

- Only do AFB smears, no cultures
- Poor Drug Susceptibility testing, physicians do not trust or act on results
- Poor Turn around time for lab results, too late to act upon, client spreading disease while waiting for results

Causes of Inadequate Treatment Pharmacy

- Poor quality of medications
- Poor storage conditions, become spoiled
- Wrong dose or combination
- Lack of availability
  - Delivery disruption
  - Lack of continuous supply

WHO 2008

Patient Factors which create Drug Resistance

- Patient not taking all of the prescribed drugs
  - Misunderstanding on how to take the meds
  - Intolerance or toxicity of the meds
  - Not believing in the diagnosis of TB
  - Not believing in the need or effectiveness of therapy
  - Chaotic life style
  - Substance abuse
  - Psychiatric disease
  - No money to pay for the medications
  - Lack of transportation to get to the clinics

WHO 2008

What are we doing in VA to prevent Drug Resistant TB?

- Use of Nucleic Acid Amplification to detect presence of Mycobacterium TB Complex in sputum specimens of new TB clients
  - Prevent treatment of clients with Non Mycobacterial Tuberculosis with wrong meds.
  - Use resources to take care of the most infectious TB clients
  - Use resources to initiate Contact Investigations

Performance of Gen-Probe MTD and Roche Amplicor M. tb Test Direct

	Smear + (%)	Smear – (%)
Sensitivity	95-96	48-53
Specificity	100	96-99
PPV	100	24-58
NPV	86-90	99

What else are we doing

- CDC has a new service to do molecular beacon testing on TB cultures
  - This tests for genetic abnormalities in the MTC which are associated with drug resistance
  - These tests take less than a week and give the likelihood of drug resistance by finding abnormalities in the genome of the MTC

South Africa-536 specimens

TABLE 3. PERFORMANCE OF GENOTYPE MTBDR*plus* IN DETECTING RIFAMPICIN, ISONIAZID, AND MULTIDRUG RESISTANCE FROM SMEAR-POSITIVE SPUTUM SPECIMENS

	Rifampicin	Isoniazid	Multidrug Resistance
Sensitivity	98.9 (94.3–100.0)	94.2 (88.4–97.6)	98.8 (93.7–100.0)
Specificity	99.4 (98.0–99.9)	99.7 (98.3–100.0)	100 (99.0–100.0)*
Overall accuracy	99.3 (98.1–99.9)	98.2 (96.5–99.2)	99.8 (98.8–100.0)
PPV	97.9 (92.7–99.7)	99.1 (95.3–100.0)	100 (95.8–100.0)*
NPV	99.7 (98.5–100.0)	97.9 (95.8–99.2)	99.7 (98.5–100.0)

Definition of abbreviations: NPV = negative predictive value; PPV = positive predictive value.

Spain-54 Specimens

Table 3 Sensitivity and specificity of the GenoType MTBRplus assay

	Sensitivity			Specificity		
	Strains	Sputum smear samples	Total	Strains	Sputum smear samples	Total
RMP-R*	100	100	100	100	100	100
INH-R*	93.1	100	96.5	91.7	100	95.8
MDR	94.7	100	97.3	95.5	100	97.7

*MDR strains and samples are included in RMP-R and INH-R for sensitivity and specificity calculations.
RMP = rifampicin; R = resistant; INH = isoniazid; MDR = multidrug-resistant.

GenoTypeMTBDR*plus*

Smear Negative specimens

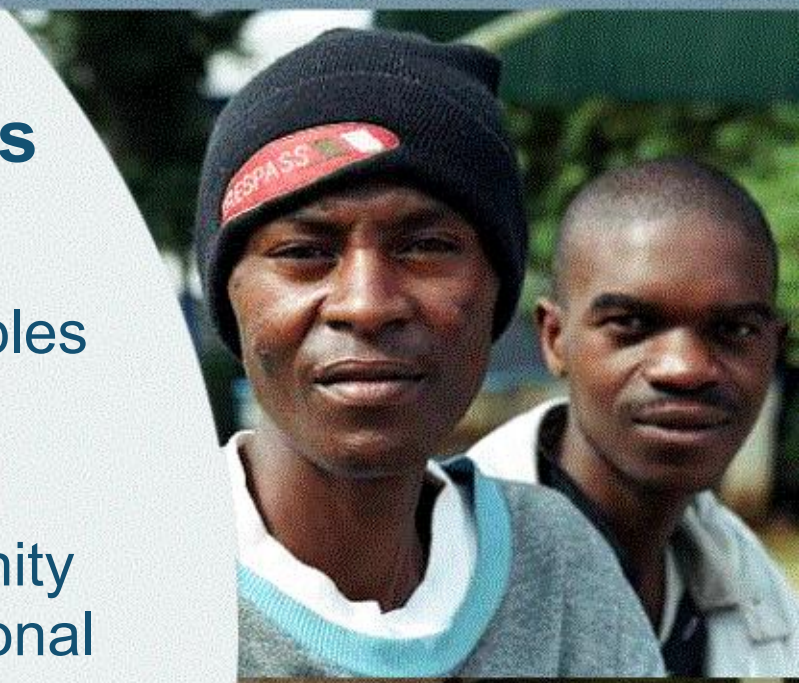
- If culture was negative, MTBDR was neg.
- Three cultures were contaminated and MTBDR gave results
- Twenty-five cultures were positive and drug susceptibility testing was done on 20.
  - 80% gave interpretable MTBDR results for RIF
  - 74% gave MTBDR results for INH!

Value with HIV patients-usually with low bacillary loads

Patient-centered DOT

More Than Watching Patients Swallow Their Pills

- DOT is a support system that enables the completion of the long, difficult course of MDR-TB treatment.
- A patient requires respect and dignity regardless of social class, educational level or unhealthy behaviors.
- The whole patient, lifestyle and support system are assessed and routinely addressed in the delivery of care.
- Goal: Inspire and empower patient via a relationship of trust and support.



Your Role

- You see the client the most.
- Develop a trusting relationship, by being able to answer their questions and if you do not know, check with the PHN
- Ask about potential drug side effects and be ready to share your knowledge about them and how to alleviate them or ask your PHN for assistance

Your Role in Preventing Drug Resistance

- Know what medications have been prescribed for your client
- Check that they are the correct meds and doses
- Teach your client about TB and why 6 months or more is needed to cure M. tb disease; get feedback to be sure the client understands what you are teaching

Your Role

- Build a relationship with your client
- Learn what their worries and concerns are
- Try to help alleviate those worries and enlist the PHN Manager to help
- Learn about their support system
- Learn where they may go if they flee

What we did today

- Learned what is Drug Resistant TB
- Learned where DR TB came from
- Learned your role in preventing it